UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,597	11/21/2003	Natalie C. Twine	WYE-021	3640

54623 7590 09/11/2007

KIRKPATRICK & LOCKHART PRESTON GATES ELLIS LLP
(FORMERLY KIRKPATRICK&LOCKHART NICHOLSON GRAHAM)
STATE STREET FINANCIAL CENTER
ONE LINCOLN STREET
BOSTON, MA 02111-2950

EXAMINER	
LIU, SUE XU	
ART UNIT	**PAPER NUMBER**
1639	

MAIL DATE	DELIVERY MODE
09/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/717,597	TWINE ET AL.	
	Examiner	Art Unit	
	Sue Liu	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8 and 21-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8 and 21-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/8/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Claims 2 and 9-20 have been canceled as filed on 6/8/07.

Claims 21-30 have been added as filed on 6/8/07.

Claims 1, 3-8 and 21-30 are currently pending.

Claims 1, 3-8 and 21-30 are being examined in this application.

Election/Restrictions

2. Applicant's elected the following species by original presentation in the reply field on 11/7/05 is as previously acknowledged:

A.) Gene TLR2;

B.) SEQ ID NO. 1;

C.) CPS No. 1 (2325-2635 of SEQ ID NO: 1);

D.) SEQ ID NO: 240.

3. Applicants have added new claims 21-30 and are examined in the instant application.

Priority

4. This application claims priority to provisional applications 60/427,982 filed on 11/21/2002, and 60/459,782 filed on 04/03/2003.

5. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or

more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/427,982, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, the said provisional application does not provide support for Table 6, which does not obtain the benefit of the priority date (11/21/2002) of the provisional application.

Thus, the effective filing date for the said subject matter is 4/3/03.

Claim Rejections Withdrawn

6. In light of applicants' amendments to the claims, the following claim rejections as set forth in the previous office action are withdrawn:

Claims 1, 3-8, 12, 13 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Rejection

8. Claims 1, 3-8 and 21-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The previous rejection is maintained for the reasons of record as set forth in the previous Office action. The rejection over claims 12, 13 and 15 is moot due to applicant's cancellation of the said claims. The rejection over claims 21-30 is necessitated by applicant's amendment to the claims.

The instant claims recite a method for diagnosis of renal cell carcinoma (RCC), the method comprising the steps of: (a) providing at least one peripheral blood sample of a human; (b) generating an expression profile comprising expression levels of one or more RCC disease genes in said at least one peripheral blood sample; (c) comparing the expression profile generated in step (b) to at least one reference expression profile comprising expression levels of said one or more RCC disease genes, wherein the comparison is indicative of the presence or absence of RCC in the human, and wherein said one or more RCC disease genes are selected from the group consisting of: eukaryotic elongation factor 1 alpha 2 (EEF1A2); toll-like receptor

2 (TLR2); zinc finger protein 36, C3H type-like 2 (BRF2); lectin, galactoside-binding, soluble, 3 (LGALS3); small nuclear ribonucleoprotein polypeptide G (SNRPG); Ras-induced senescence 1 (DKFZP586E1621); nuclear mitotic apparatus protein 1 (NUMA1); superoxide dismutase 2 (SOD2); aldo-keto reductase family 1, member B1 (AKR1B1); dual specificity phosphatase 6 (DUSP6); SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily e, member 1 (SMARCE1); KIAA0669; MLL septin-like fusion (MSF); interleukin 1 receptor antagonist (IL1 RN); prothymosin, alpha (PTMA); KIAA0410; proteasome 26S subunit, non-ATPase, 3 (PSMD3); T54 protein (T54); complement component 1, q subcomponent binding protein (C1QBP); and oxidative-stress responsive 1 (OSR1).

To satisfy the written description requirement, applicants may convey reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

Applicants may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. See, e.g., Vas-Cath, 935 F.2d at 1565, 19 USPQ2d at 1118.

The written description requirement of 35 U.SC. 112 exists independently of enablement requirement, and the requirement applies whether or not the case involves questions of priority. The requirement applies to all inventions, including chemical inventions, and because the fact that the patent is directed to method entailing use of compound, rather than to compound per se, does not remove patentee's obligation to provide a description of the compound sufficient to distinguish infringing methods from non-infringing methods. See Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 920-23, 69 USPQ 2d 1886, 1890-93 (Fed. Cir. 2004).

With regard to the description requirement, applicants' attention is invited to consider the decision of the Court of Appeals for the Federal Circuit, which holds that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it form other materials." University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1405 (1997), quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original) [The claims at issue in University of California v. Eli Lilly defined the invention by function of the claimed DNA (encoding insulin)].

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species or by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical an/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F. 3d at 1568, 43 USPQ2d at 1406.

The instant claims are drawn to a method using a genus of genes for diagnosing (i.e. indicating "the presence or absence of RCC in the human") RCC. The broad independent Claim 1 is drawn to a genus of genes and/or any combination thereof, and a genus of "expression profiles" (including both individual genes or any combination thereof). Neither the instant specification nor the claims have demonstrated common structure and/or function for the claimed genus of genes and the genus of gene expression profiles that can be used to diagnose RCC

specifically. In addition, no representative numbers of species for each claimed genus is provided to show possession of the claimed genus of genes and genus of expression profiles.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. (see MPEP 2163 II).

In this case, the instant application does not specifically disclose which individual genes or combination thereof would provide gene expression profiles that can be used to diagnose RCC specifically. In addition, some of the genes listed in the specifications (such as the ones listed in Tables 4 and 6) are also known to be indicative of other cancers (e.g. [0150], [0214], [0269], etc.). For example, the so called TLR2 gene is known in the art to be over-expressed in individual with immunoactivation such as bacterial infection (see Liu et al., Infection and Immunity. Vol. 69(5): 2788-2796; 2001; cited previously). Anand et al (Nature Genetics. Voll. 31: 301-305; 2002) teach the overexpression of the EEF1A2 gene is observed in ovarian cancer tumors (see Abstract of Anand). It is not known in the art that all genes listed in the instant claim 1 are "differentially expressed" in RCC patient as compared to other diseased individual. That is at least for the methods of specifically diagnosing RCC using the expression profiles of individual genes are highly unpredictable.

The instant specification only provides examples (e.g. Example 6) where the expression profiles of genes from RCC patient are compared to diseases free individuals, but not to patients with other diseases. In addition, the instant specification only provides examples of correlating

gene expression profiles from RCC patients with tumors (i.e. later stage of RCC) to disease free individuals. The instant specification does not provide support for the entire claimed genus of methods of "diagnosing" RCC at any stage of the disease. That is applicants have not shown the correlation observed between gene expression profiles of RCC tumor and disease free tissues are predictive to "diagnosis" of RCC at any stage of the disease or to differentiating RCC from other diseases.

Thus, applicants do not appear to have possession of the entire claimed genus of methods of using any one or more of the listed "RCC disease genes" for specifically diagnosing RCC. One of ordinary skilled in the art would not be able to specifically diagnose RCC based on any individual gene expression and/or combination thereof of the listed genes. Without generating the desired gene expression profile, the claimed method of diagnosis cannot be accomplished.

Furthermore, the instant claims recite gene(s) by using gene names as listed in "Table 4" or "Table 6", which do not clearly indicate the required sequences for the claimed method (especially Table 6). The genes listed in Table 6 recite genes by their GenBank accession number, name, and Unigene ID. However, GenBank and Unigene ID do not provide stable and unchanging source of information. For example, Table 6 does not specifically identify the exact polynucleotide sequences that can be used for gene expression profiling. GENBANK information may be updated and revised anytime (see http://www.ncbi.nih.gov/Genbank/index.html under the heading Updating or Revising a Sequence; GenBank Printout, downloaded 2/21/07; cited previously), therefore, the claimed sequences could change anytime. A search of the UNIGENE ID reveals that many of the Ids have been "retired" and contain zero sequence (e.g. Hs.63668 for TLR2; See UNIGENE

Printout, downloaded 2/21/07; cited previously). In addition, many genes listed in Table 4 have DNA sequences (e.g. SEQ ID 22 has >300 "n" positions out of 870 total) comprising numerous ambiguous positions designated as "n", which can be any nucleotides. These would result in an enormous number of nucleic acid sequences. Thus, one of ordinary skill in the art would not be able to perform the recited invention using the sequences provided, and applicants do not appear to possess the claimed genus of methods using these claimed genes.

Applicants also do not possess the entire genus of gene expression profiles for diagnosing or indicating the "presence or absence of RCC in the human". As stated in the instant specification, the genes listed in Tables 4 and 6 may also be differentially expressed in patients with other diseases than RCC. (e.g. [0045]). The instant specification also states "it is suggestive that the human subject may be infected with RCC (or other solid tumors, depending on the genes used in the diagnosis)" ([0492]), which indicates that further experimentation is needed to distinguish RCC from other diseases using gene expression profiles. Thus, it is highly unpredictable to use various genes and their expression profiles for diagnosing RCC. Although the instant specification teach one example of using a 20-gene set to differentiate RCC from certain other tumors (Example 8), the instant specification does not provide all possible combination of genes or individual genes (from the claimed list) that can be used to differentiate RCC from other tumor diseases. For example, an over expression of one single gene (such as TLR-2) may not create an expression profile to distinguish among different diseases. As evidenced by the instant specification, only one relative successful indication of RCC was achieved based on one expression profile generated from at least 20 genes (Example 8). In addition, data in Table 6 (and [0589] of the spec.) indicates that at least 16 genes are presented

only in one sample (a single patient), and more genes are only presented in few than 6 patients (~10% of total sample size), which would not be representative or statistically significant to show possession of the claimed method. This also indicates high unpredictability of using these genes for diagnosing RCC in any human.

As discussed above, only one example of a method based on one 20-gene set is not representative number of species for the claimed method using different genes (from the 20-gene example) or sequences and any combination thereof. Furthermore, the specific sequences of the claimed genes are not all known, which the sequences are required to perform the claimed method.

Thus, applicant's claimed scope represents only an invitation to experiment regarding possible genes and gene expression profiles that might be used for the purpose of indicating the presence and absence of RCC in human.

Therefore, applicants are not in possession of a claimed genus of "RCC disease genes" and the various gene expression profiles as well as the genus of methods that are using the various gene expression profiles to diagnose RCC. Applicant's claimed scope represents only an invitation to experiment regarding possible genes and gene expression profiles that might be used for the purpose of indicating the presence and absence of RCC in human.

Discussion and Answer to Argument

9. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue the claim amendment is sufficient to overcome the previously set forth written description rejection. (Reply, pp. 5-6).

However, applicant's amendments to the claims are not sufficient to overcome the written description rejection as set forth previously as well as the reasons discussed above.

Scope of Enablement Rejection

10. Claims 1, 3-8 and 21-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the gene expression profile of the combination of the 20 genes listed in Table 10 (Example 8) to indicate RCC at the tumor stage when compared to the gene expression profiles of disease free individuals, does not reasonably provide enablement for using any other genes or combination of genes and their expression profiles for the purpose of indicating the presence and absence of RCC in any human (such as the ones with other diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The previous rejection is maintained for the reasons of record as set forth in the previous Office action. The rejection over claims 12, 13 and 15 is moot due to applicant's cancellation of the said claims. The rejection over claims 21-30 is necessitated by applicant's amendment to the claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. §112, first paragraph, have been described *In re Wands*, 8 USPQ2d 1400(1988). They are:

1. The breadth of the claims;
2. The nature of the invention;

3. The state of the prior art;
4. The predictability or lack thereof in the art
5. The level of skill in the art;
6. The amount of direction or guidance present;
7. The presence or absence of working examples;
8. The quantity of experimentation needed.

The breadth of the claims / The nature of the invention

The instant claims are drawn to a method using a genus of genes and/or combination thereof for diagnosing (i.e. indicating "the presence or absence of RCC in the human") RCC. The broad independent Claim 1 is drawn to a genus of genes and/or any combination thereof, and a genus of "expression profiles" (including both individual genes or any combination thereof).

The state of the prior art/ The predictability or lack thereof in the art

The instant application does not specifically disclose which individual genes or combination thereof would provide gene expression profiles that can be used to diagnose RCC specifically. In addition, some of the genes listed in the specifications (such as the ones listed in Tables 4 and 6) are also known in the art to be indicative of other cancers (e.g. [0150], [0214], [0269], etc. of the instant specification). For example, the so called TLR2 gene is known in the art to be over-expressed in individual with immunoactivation such as bacterial infection (see Liu et al., Infection and Immunity. Vol. 69(5): 2788-2796; 2001; cited previously). Anand et al (Nature Genetics. Voll. 31: 301-305; 2002) teach the over-expression of the EEF1A2 gene is

observed in ovarian cancer tumors (see Abstract of Anand). That is an observation of over-expression of TLR2 and/or EEF1A2 can be indicative of other diseases than RCC. The art does not provide teaching to indicate how to distinguish among the different diseases (e.g bacterial infection, ovarian cancer, RCC, etc.) based on the gene expression profile of the said genes. It is not known in the art that all genes listed in the instant claim 1 are "differentially expressed" in RCC patient as compared to other diseased individual. That is at least for the methods of specifically diagnosing RCC using the expression profiles of individual genes are highly unpredictable.

Furthermore, the instant claims recite gene(s) by using gene names as listed in the instant specification such as the ones listed "Table 4" or "Table 6", which do not clearly indicate the required sequences for the claimed method (especially Table 6). The genes listed in Table 6 recite genes by their GenBank accession number, name, and Unigene ID. However, GenBank and Unigene ID do not provide stable and unchanging source of information. For example, Table 6 does not specifically identify the exact polynucleotide sequences that can be used for gene expression profiling. GENBANK information may be updated and revised anytime (see http://www.ncbi.nih.gov/Genbank/index.html under the heading Updating or Revising a Sequence; GenBank Printout, downloaded 2/21/07; cited previously), therefore, the claimed sequences could change anytime. A search of the UNIGENE ID reveals that many of the Ids have been "retired" and contain zero sequence (e.g. Hs.63668 for TLR2; See UNIGENE Printout, downloaded 2/21/07; cited previously). In addition, many genes listed in Table 4 have DNA sequences (e.g. SEQ ID 22 has >300 "n" positions out of 870 total) comprising numerous ambiguous positions designated as "n", which can be any nucleotides. These would result in an

enormous number of nucleic acid sequences. Thus, one of ordinary skill in the art would not be able to perform the recited invention using the sequences provided.

To further indicate the unpredictability of the instant claimed method, the instant specification also states "it is suggestive that the human subject may be infected with RCC (or other solid tumors, depending on the genes used in the diagnosis)" ([0492]), which indicates that further experimentation is needed to distinguish RCC from other diseases using gene expression profiles. Thus, it is highly unpredictable to use various individual genes and/or combination thereof, and their expression profiles for diagnosing RCC. Although the instant specification teach one example of using a 20-gene set to differentiate RCC from certain other tumors (Example 8), the instant specification does not provide all possible combination of genes or individual genes (from the claimed list) that can be used to differentiate RCC from other tumor diseases. For example, an over expression of one single gene (such as TLR-2) may not create an expression profile to distinguish among different diseases. As evidenced by the instant specification, only one relative successful indication of RCC was achieved based on one expression profile generated from at least 20 genes (Example 8). In addition, data in Table 6 (and [0589] of the spec.) indicates that at least 16 genes are presented only in one sample (a single patient), and more genes are only presented in few than 6 patients (~10% of total sample size), which would not be representative or statistically significant to show possession of the claimed method. This also indicates high unpredictability of using these genes for diagnosing RCC in any human.

As discussed above, only one example of a method based on one 20-gene set is not representative number of species for the claimed method covering at least a few hundred genes

(or sequences) and almost infinite number of combinations of the genes. Furthermore, the specific sequences of the claimed genes are not all known, which the sequences are required to perform the claimed method.

The above discussion only illustrated a few problems performing the claimed methods of diagnosing RCC using gene expression profile. Although there may be suggested methods of overcoming these problems through non-routine experimentations, there are no predictable methods or solutions that would solve all the problems for any gene, or combination of genes.

The level of one of ordinary skill

The level of skill would be high, most likely at the Ph.D. level.

The amount of direction or guidance present / The presence or absence of working examples

As discussed above, the instant specification recite an example of using a 20-genes set to predict with certain percent accuracy (such as 89%) for RCC disease when comparing gene expression profiles between RCC patient and patient with certain other tumors. (see Example 8 of the instant specification).

The instant specification also provides examples (e.g. Example 6) where the expression profiles of genes from RCC patient are compared to diseases free individuals, but not to patients with other diseases. In addition, the instant specification only provides examples of correlating (but not "diagnosing") gene expression profiles from RCC patients with tumors (i.e. later stage of RCC) to disease free individuals. The instant specification does not provide support for the entire claimed genus of methods of "diagnosing" RCC at any stage of the disease. That is

applicants have not shown the correlation observed between gene expression profiles of RCC tumor and disease free tissues are predictive to "diagnosis" of RCC at any stage of the disease.

The quantity of experimentation needed

Due to the unpredictabilities of the using gene expression profiles of various genes or combinations of genes to diagnosis for a specific disease such as RCC as discussed above, undue experimentation would be required. The art has not demonstrated all the possible genes or combinations of genes as well as their specific expression profiles that can be used to specifically diagnose RCC as discussed above. Because the instant specification only provides guidance for one example of using a specific combination of a 20-genes set for specific diagnosis of RCC, undue experimentation would be required to practice claimed method of diagnosis based on various gene expression profiles.

Conclusion

Due to the non-routine experimentation necessary to determine the specific genes and their expression profiles for diagnosing RCC; the lack of direction/guidance presented in the specification regarding the specific requirements for the method; the unpredictability of the selection method for enzymes with particular catalytic activities as established by the state of the prior art; the breadth of the claims, undue experimentation would be required of a skilled artisan to make and/or use the claimed invention in its full scope.

Discussion and Answer to Argument

11. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue the claim amendment is sufficient to overcome the previously set forth Scope of Enablement Rejection. (Reply, pp. 6-7).

However, applicant's amendments to the claims are not sufficient to overcome the scope of enablement rejection as set forth previously as well as the reasons discussed above. Applicants are respectively directed to the above discussion for additional answer to arguments.

New Claim Rejections

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter Rejection

13. Claims 1, 3-8 and 21-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is necessitated by applicant's amendments to the claims.

Claim 1 has been amended to recite methods of using the gene expression profiles of "one or more" RCC disease genes such as the "eukaryotic elongation factor 1 α 2", "zinc finger protein 36", "C3H type-like 2", "small nuclear ribonucleoprotein polypeptide G", etc., for the specific diagnosis of RCC disease. However, the instant specification does not provide support for the method of using any one or any combination of the recited genes in the amended claims.

Applicants have provided "Table 4 and the paragraphs following" as citation for support of the newly added claim limitations. However, neither Table 4 nor the "paragraphs following" provide support for the claimed methods of using the specific genes for diagnosing RCC specifically.

If Applicant believes this rejection is in error, applicant must disclose where in the specification support for the entire scope of the amendment(s) and/or new claims can be found. As a result, Claims 1, 3-8 and 21-30 represents new matter.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(Note: the instant claim numbers are in bold font.)

15. Claims 8-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over McKiernan et al (US 6,087,098; 7/11/2000; cited in IDS), in view of Young et al (American Journal of

Pathology. Vol. 158(5): 1639-1651; 5/2001), Golub et al (Science. Vol. 286: 531-527; 1999; cited previously) and Liu et al (Infection and Immunity. Vol. 69: 2788-2796; 2001; cited previously). This rejection is necessitated by applicant's amendments to the claims.

The instant claims recite a method for diagnosis of renal cell carcinoma (RCC), the method comprising the steps of: (a) providing at least one peripheral blood sample of a human; (b) generating an expression profile comprising expression levels of one or more RCC disease genes in said at least one peripheral blood sample; (c) comparing the expression profile generated in step (b) to at least one reference expression profile comprising expression levels of said one or more RCC disease genes, wherein the comparison is indicative of the presence or absence of RCC in the human, and wherein said one or more RCC disease genes are selected from the group consisting of: eukaryotic elongation factor 1 alpha 2 (EEF1A2); toll-like receptor 2 (TLR2); zinc finger protein 36, C3H type-like 2 (BRF2); lectin, galactoside-binding, soluble, 3 (LGALS3); small nuclear ribonucleoprotein polypeptide G (SNRPG); Ras-induced senescence 1 (DKFZP586E1621); nuclear mitotic apparatus protein 1 (NUMA1); superoxide dismutase 2 (SOD2); aldo-keto reductase family 1, member B1 (AKR1B1); dual specificity phosphatase 6 (DUSP6); SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily e, member 1 (SMARCE1); KIAA0669; MLL septin-like fusion (MSF); interleukin 1 receptor antagonist (IL1 RN); prothymosin, alpha (PTMA); KIAA0410; proteasome 26S subunit, non-ATPase, 3 (PSMD3); T54 protein (T54); complement component 1, q subcomponent binding protein (C1QBP); and oxidative-stress responsive 1 (OSR1).

McKiernan et al, throughout the patent, the methods of diagnosing prostate cancer using peripheral blood samples (Abstract). The reference teaches measuring gene expression level

from samples isolated from peripheral blood sample (e.g. Abstract; col.2, lines 62+), which reads on steps (a) and (b) of the **clm 1** as well as the whole blood sample of **clm 4**. The reference also teaches comparing gene expression profile of the sample with the expression profile of samples from normal individuals (e.g. col.2, lines 39+), which reads on step (c) of **clm 1**.

The reference also inherently teaches "the peripheral blood sample" comprises enriched peripheral blood mononuclear cells as recited in **clm 3**, because peripheral blood sample inherently comprise mononuclear cells as evidenced by Ralph et al (US 6,190,857; 2/20/2001; cited previously; claim 3 and col.94, lines 20+).

The reference also teaches "preparing cDNA from the mRNA" (e.g. col.2, liens 65+) and "reverse transcriptase-PCR" (RT-PCR) assay (e.g. cols. 1-2; bridging para), which reads on the RT PCR of **clm 5**.

The reference also teaches the normal samples are obtained from the peripheral blood of normal individuals as well as patients with RCC (e.g. col.2, lines 50+), which reads on the limitation of **clms 6** and **7**.

McKiernan et al do not explicitly teach the specific listed "RCC disease genes" as recited in **clms 1** and **21-30**.

However, **Young** et al, throughout the publication, teach using gene expression profiling for diagnosis or classification of renal cell carcinomas (Abstract). The reference teaches various genes that are differentially expressed in RCC when compared to normal kidney tissues (e.g. Figure 1). The reference teaches "Galectin 3" is differentially expressed in RCC and can be used for diagnosis and classification purposes (e.g. p. 1640, col.1, para 2), which reads on the gene listed in **clms 1** and **22-30**.

Golub et al, throughout the reference, teach cancer classification based on gene expression by using statistical analysis including weighted voting algorithm (See Abstract and Page 532, right column, first paragraph), which reads on the weighted voting algorithm of **clm 8**. The reference also teaches the advantages of using these statistical tools to analyzing gene expression profiles such as "class predictors can be constructed for known pathological categories-reflecting a tumor's cell of origin, stage, or grade. Such predictors could provide diagnostic confirmation or clarify unusual cases."

Liu et al, throughout the reference, teach TLR2 is predominantly distributed in monocytes/macrophages (refers to mononuclear cells; See page 2788, left column, 2nd paragraph), which reads on one or more genes (TLR2) listed in **clms 1, 8 and 21**. The reference also teaches that TLR2 is involved in the signal pathway of NF-κB of the immunosystem. The reference also teaches isolating monocytes (reads on PBMCs) by centrifugation from blood of healthy donors (See Page 2789, right column, 1st paragraph).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to generate a method comprising comparing gene expression profile of one or more genes (specifically TLR2 gene) from peripheral blood samples using known statistical tools to analyze the expression pattern.

Because Young et al teach "Galectin 3" gene is differentially expressed in RCC patients as compared to normal individuals, a person of ordinary skill in the art would have been motivated at the time of the invention to use Galectin 3 gene expression profile for diagnosis of RCC.

Because Golub et al teach classification based on gene expression profile with weighted voting algorithm is useful in cancer diagnosis and offers an advantage for diagnosis of unusual cases, a person of ordinary skill in the art would have been motivated at the time of the invention to use the statistical analysis taught by Golub et al to process gene expression profile data generated by comparing differential gene expression between diseased and normal humans.

Because Liu et al teach that TLR2 is expressed in PBMCs and involved in the tumor signal pathway of NF-κB of the immunosystem as discussed supra, one of ordinary skilled in the art would have been motivated at the time the invention was made to compare the gene expression profile from patients and disease-free humans using genes that are know to be expressed in PBMCs, and are also known to be involved in the tumor signal pathway. In addition,

Because the statistical methods are known and are successfully used for comparing differential gene expression profile in cancer patients as taught by Golub et al, an ordinary skilled artisan would have reasonable expectation of success of achieving such modifications. Because methods for monitoring gene expression profiles (for various genes) are known in the art as demonstrated by Young et al and Liu et al, and the differentially expressed genes (such as TLR2 and Galectin 3) are known in the art as taught by Young et al and Liu et al, an ordinary skilled artisan would have reasonable expectation of success of achieving such modifications.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SL
Art Unit 1639
8/20/07

/Jon D. Epperson/
Primary Examiner, AU 1639